

## CLINICAL UPDATE

From the Society for Vascular Surgery

# Pharmacologic risk factor management in peripheral arterial disease: A *vade mecum* for vascular surgeons

Thomas F. Rehring, MD, Ryan S. Stolcpart, PharmD, and H. Whitton Hollis Jr, MD, Denver, Colo

There is broad and compelling evidence for risk factor reduction to limit cardiovascular morbidity and mortality in patients with peripheral arterial disease. Indeed, vascular surgeons have placed a call to arms to ensure this takes place. Despite this fact, some wariness exists on the part of many vascular surgeons to initiate these strategies, functionally abnegating their responsibilities in this regard. The purpose of this article is to provide a simple reference to guide effective therapies for overall cardiovascular risk reduction in patients with peripheral arterial disease. Specific recommendations are made for tobacco cessation, lipid-lowering therapy, antiplatelet therapy, blood pressure control, and maintenance of normoglycemia. (J Vasc Surg 2008;47:1108-15.)

The systemic ravages of atherosclerosis impact significantly on patients with peripheral arterial disease (PAD), who incur an annual risk of a cardiovascular event of 5% to 7%.<sup>1</sup> The presence of PAD, even in the absence of a history of coronary artery disease (CAD), confers the same relative risk of a death from cardiovascular cause as in patients with a previous cardiovascular event.<sup>2,3</sup> As such, PAD is considered a CAD equivalent, and the American Heart Association (AHA), National Heart, Lung and Blood Institute, and the National Cholesterol Education Program (NCEP) recommend identical atherosclerotic risk reduction strategies for PAD and CAD patients.<sup>4-6</sup> Risk factor modification includes therapeutic lifestyle changes, antiplatelet therapy, lipid modification, control of hypertension, smoking cessation, and glycemic control in diabetic patients.

Although these tenets are understood well and even promoted<sup>7-9</sup> by vascular surgeons, there is significant ease in initiating specific medical therapies.<sup>10,11</sup> The purpose of this article is to provide a simple reference to initiate treatment for overall cardiovascular risk reduction in patients with PAD. Specific recommendations are made for

tobacco cessation, lipid-lowering therapy, antiplatelet therapy, blood pressure control, and maintenance of normoglycemia.

### THERAPEUTIC LIFESTYLE CHANGES

All patients with PAD should undergo lifestyle modifications to limit their overall cardiovascular risk, as suggested by the AHA.<sup>12</sup> Such maneuvers include consumption of an overall healthy diet, weight loss to achieve a target body mass index <25, reductions in dietary total and saturated fat, and daily aerobic exercise. Weight loss provides decreases in low-density lipoprotein (LDL) cholesterol up to 40%, reduces serum triglycerides by 22%, and raises high-density lipoprotein (HDL) by as much as 9%.<sup>13</sup> Randomized data show that diet and exercise reduce lipid levels<sup>14,15</sup> and cardiovascular events<sup>16</sup>; however, most patients will require additive pharmacotherapy to achieve goals for blood pressure<sup>17</sup> and lipids.<sup>4</sup>

### Tobacco dependence

**Background for intervention and therapeutic goals.** More than 80% of patients with PAD are current or former smokers.<sup>18</sup> Smoking cessation decreases the mortality rate by more than one-third in patients with CAD.<sup>19,20</sup> Indeed, the benefit of *quitting* smoking on mortality reduction is likely greater than the other risk management strategies that will be discussed. In contrast, smoking *reduction* does not appear to reduce all-cause mortality.<sup>21</sup> In fact, smoking as few as 1 to 4 cigarettes a day substantially increases the risk of cardiovascular and all-cause mortality.<sup>22</sup> Clearly, the goal for PAD patients who smoke is complete and lifelong cessation.

From the Division of Vascular and Endovascular Surgery, Department of Vascular Therapy, Colorado Permanente Medical Group and the University of Colorado Health Sciences Center.

Competition of interest: none.

Presented at the Society for Vascular Surgery Annual Meeting, Baltimore, Md, Jun 8-10, 2007.

Correspondence: Thomas F. Rehring, MD, Department of Vascular Therapy, 20th Ave Medical Center, 2045 Franklin St, Denver, CO 80205 (e-mail: [trehring@msn.com](mailto:trehring@msn.com)).

0741-5214/\$34.00

Copyright © 2008 by The Society for Vascular Surgery.

doi:10.1016/j.jvs.2007.12.033

**Table I.** Pharmacotherapeutic agents for smoking cessation

	<i>Bupropion SR</i>	<i>Varenicline</i>
	<i>7-12 wks</i>	<i>12 wks</i>
Treatment period		
Details	Take for 1-2 wks before quitting; may use for maintenance for up to 6 months	Take for 1 wk before quitting; may use for maintenance for up to 6 months
Dosage	Days 1-3: 150 mg q day; days 4-end: 150 mg BID	Days 1-3: 0.5 mg q day; days 4-7: 0.5 mg BID; days 7-end 1 mg BID
Pros	Easy to use; reduces urge to smoke	Easy to use; reduces urge to smoke
Cons	May disturb sleep, may cause dry mouth	30% of patients experience nausea; should be taken with food; may disturb sleep
Caution	Do not use if seizure disorder, an eating disorder, or are taking a monoamine oxidase inhibitor	Reduce dose if creatine clearance <30 mL/min
Availability	Prescription only	Prescription only
Cost/day for average use <sup>a</sup>	\$2.33	\$3.57

BID, Twice daily; q, once daily.

<sup>a</sup>Values obtained from drugstore.com.

**Treatment.** Critical components of a successful tobacco cessation strategy include patient motivation, recurrent and timely physician advice (at each visit), behavioral therapy, and pharmacotherapy. Vascular surgeons have a unique opportunity to initiate cessation strategies. Patients often present to us in a vulnerable state, concerned over a life- or limb-threatening disorder. Reinforcement of the pernicious effects of smoking and its association with progression of disease, limb loss, and death may be particularly motivating under these conditions.

**Behavioral therapy.** Perhaps surprisingly to us as surgeons, tobacco dependence counseling is quite successful in helping patients quit smoking, whether administered in an individual, group, or telephone setting. Its effectiveness increases directly with duration of treatment time, but as little as 3 minutes of counseling helps patients quit.<sup>23,24</sup> It is increasingly available at little or no cost through local communities, insurers, and managed care organizations. These sessions may include education, suggestions for tapering, and various coping mechanisms for assistance with

relapse prevention. Quit rates at 1 year are approximately 20% for patients who complete a program<sup>25-27</sup>; however, maximal quit rates are obtained when a multimodality approach is used. In addition to behavioral therapy, all smokers should be offered one of six medications with an established empiric record of efficacy in smoking cessation (Table I).

### Pharmacotherapy

**Nicotine replacement therapy.** Nicotine is a potent psychoactive drug. After long-term use, its absence leads not only to the loss of the euphoric effects of the drug but also to symptoms of withdrawal. These may include dysphoria, depression, insomnia, anxiety, irritability, restlessness, and weight gain. Nicotine replacement therapy (NRT) helps curb some of these symptoms while the patient is undergoing concurrent behavioral therapy. Nicotine replacement therapy is safe<sup>28</sup> and does not increase cardiac risk even in patients who continue to smoke while using the patch.<sup>29</sup> Nicotine replacement therapy does not induce platelet aggregation, elevations in fibrinogen, coro-

Table I. Continued.

<i>Nicotine replacement therapy</i>			
<i>Patch</i>	<i>Gum/lozenge</i>	<i>Inhaler</i>	<i>Nasal spray</i>
6-8 wks	Up to 12 wks (May use for longer time as needed)	3-6 wks	3-6 wks
Treatment period		Taper use over last few weeks	Taper use over last few weeks
One patch/d; taper dose if using: 21 mg for 4 wks; 14 mg for 2 wks; 7 mg for 2 wks. No taper if using 15 mg for 8 wks; light smokers (10 cig/d) can start with lower dose	2 mg; 4 mg (heavy smokers); 1 piece every 1-2 h (10-15 pieces/d); many do not use enough	6-16 cartridges/d; need to inhale about 80 times to use up cartridge; can use part of cartridge and save the rest for later that day	One dose = 1 squirt to each nostril; dose 1-2 times/h as needed; min = 8 doses/d; max = 40 doses/d
Easy to use; ready dose of nicotine	Patient controls the dose; helps with predictable urges (eg, after meals); keeps mouth busy	Patient controls the dose; helps with predictable urges; keeps hands and mouth busy	Patient controls the dose; fastest acting for relief of urges
May irritate skin; may disturb sleep; cannot adjust amount of nicotine in response to urges	Need to chew correctly—"chew and park"; should not drink acidic beverages while chewing gum	May irritate mouth and throat (improves with use); does not work well <40°; should not drink acidic beverages while using inhaler	Need to use correctly (do not inhale it); may irritate nose (improves with use); may cause dependence
Do not use if severe uncontrolled eczema or psoriasis	Caution with dentures	May induce bronchospasm, consider patch in patients with reactive airway disease	May induce bronchospasm, consider patch in patients with reactive airway disease
Over the counter	Over the counter (regular, mint, or orange)	Prescription only	Prescription only
Brand name, \$3.21; store brand, \$2.19	Brand name, \$4.50; store brand, \$2.18	\$8.22 (10 cartridges/d)	\$4.08 (12 doses/d)

nary vasospasm, myocardial ischemia, or major changes in heart rate or blood pressure that are associated with smoking.<sup>30</sup>

Nicotine replacement is available in gum, lozenge, transdermal patch, nasal spray (Nicotrol NS; Pharmacia, Helsingborg, Sweden), and inhaler (Nicotrol Inhaler, Pharmacia). All have similar efficacy in the promotion of smoking cessation, increasing the odds of quitting 1.5- to 2-fold.<sup>31</sup> This benefit occurs even in the absence of supportive behavioral therapy. Slightly higher quit rates have been demonstrated with higher doses of the patch and gum, particularly in heavier smokers. For most patients, quit rates of 40% to 60% can be expected at the conclusion of a behavior therapy program combined with NRT therapy, decreasing to 25% to 30% at 1 year.<sup>24</sup>

**Bupropion SR.** Bupropion is an atypical antidepressant with both dopaminergic and adrenergic actions. The sustained release form of the drug became available in 1998 specifically targeted at assisting with smoking cessation (Zyban; Glaxo SmithKline, Research Triangle Park, NC).

It can be used in patients who have failed or are intolerant of NRT, unaccompanied as first-line therapy, or combined with NRT.<sup>32</sup> Treatment with bupropion SR doubles quit rates at 1 year vs placebo.<sup>33</sup> Evidence suggests that monotherapy with bupropion is superior to NRT alone<sup>32</sup> and that the addition of NRT to bupropion adds little to overall efficacy.<sup>34</sup> In general, bupropion is dosed twice daily (Table I); however, once-daily dosing may be equally effective and better tolerated.<sup>35</sup> Bupropion lowers the threshold for seizures and thus is contraindicated in patients with a seizure disorder but is overall quite safe. The most common side effects are insomnia, dry mouth, and nausea.

**Varenicline.** Varenicline (Chantix; Pfizer; Mission, KS) is a partial agonist of the  $\alpha_4\beta_2$  nicotinic acetylcholine receptor. It works by stimulating dopamine release in the brain, but to a lesser degree than nicotine, and blocks nicotine from binding to the nicotine receptor. This results in relief of nicotine withdrawal symptoms and cigarette cravings as well as decreases the reinforcement and reward associated with smoking. The United States Food and

**Table II.** Comparison of lipid-lowering agents

Drug	Atorvastatin <sup>53</sup>	Fluvastatin	Lovastatin <sup>54</sup>	Pravastatin <sup>53</sup>	Rosuvastatin <sup>53</sup>	Simvastatin <sup>53</sup>
Trade name	Lipitor	Lescol	Mevacor/Altoprev	Pravachol	Crestor	Zocor
Common dose range	10-80 mg/d	20-80 mg/d	10-80 mg/d	10-80 mg/d	10-80 mg/d	5-80 mg/d
Lipid level change, %						
Total cholesterol	(-) 27-39	(-) 17-25	(-) 16-29	(-) 15-22	(-) 33-40	(-) 20-33
LDL	(-) 37-51	(-) 22-35	(-) 24-40	(-) 20-30	(-) 46-55	(-) 28-46
HDL	(+) 2-6	(+) 3-7	(+) 7-10	(+) 3-6	(+) 8-10	(+) 5-7
Triglycerides	(-) 20-28	(-) 17-25	(-) 10-19	(-) 8-13	(-) 20-26	(-) 12-18
Cost (#30, 20 mg) <sup>a</sup>	\$109.19	\$74.72	\$22.99	\$17.99	\$100.47	\$27.99

LDL, Low-density lipoprotein; HDL, high-density lipoprotein.

<sup>a</sup>Values obtained from drugstore.com.

Drug Administration (FDA) approved it for assistance with smoking cessation in May 2006. It appears to increase the chance of successful quitting nearly threefold.<sup>36</sup> In clinical studies, varenicline appears to have a slight advantage in continuous abstinence rates over bupropion SR at 3 and 6 months, but perhaps less so at later intervals.<sup>37-39</sup> In addition, 24 weeks of varenicline improves continuous abstinence rates at 6 months and 1 year compared with 12 weeks of therapy.<sup>40</sup> These benefits come at some expense: varenicline costs nearly twice as much as bupropion SR and NRT. Serious side effects are rare, and no contraindications or drug-drug interactions have been identified for varenicline. Up to 30% of patients experience mild to moderate nausea that can be reduced by taking the medication after eating or with a full glass of water.

**Recommendations.** In combination with targeted, personal physician advice and referral to behavioral therapy, we recommend bupropion SR at 150 mg/d for 3 days, then 150 mg twice daily for 7 weeks. The patient's intended quit date should be 1 week after the initiation of bupropion. Nicotine replacement therapy may be added to this regimen for the heaviest of smokers.

## Hyperlipidemia

**Background for intervention.** Epidemiologic and prospective observational cohort studies have shown a graded correlation between serum cholesterol and the risk of coronary events.<sup>41</sup> Several subsequent large, prospective randomized trials<sup>42-45</sup> and meta-analysis<sup>46</sup> have confirmed that statin use results in a 20% to 30% reduction in cardiovascular and all-cause mortality in patients with CAD.<sup>47</sup> Furthermore, statin pleiotropism in producing beneficial effects is nearly legendary, with known effects on atherosclerotic plaque stabilization and reduction in oxidative stress and vascular inflammation.<sup>48</sup>

**Therapeutic goals.** In general, recommendations for the treatment of hyperlipidemia are based upon the LDL cholesterol (LDL-C) fraction. The AHA/American College of Cardiology (ACC) guidelines published in 2006 recommend a LDL goal of <100 mg/dL for all patients with PAD.<sup>1</sup> The modified Third Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III or ATP III) guidelines, published in 2004, recommended an op-

tional LDL goal of <70 mg/dL for "very-high-risk" patients.<sup>5</sup> The 2005 ACC/AHA guidelines define "very-high-risk" PAD patients as those with multiple risk factors (especially diabetes), severe or poorly controlled risk factors (especially smoking), and risk factors of the metabolic syndrome (especially elevated triglycerides in the face of an elevated non-HDL/HDL ratio).<sup>1</sup> Moreover, a recent prospective observational cohort study of nearly 1400 PAD patients showed that intensive therapy with statins targeting an LDL <70 mg/dL improved overall and cardiac mortality at a mean follow-up of 6 years.<sup>49</sup>

Although therapeutic lifestyle changes are important to all patients, we do not believe in withholding drug therapy in patients with PAD with total cholesterol >135 mg/dL. Statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) are the only class of lipid-lowering drugs shown to decrease overall mortality in primary and secondary prevention of coronary events. The PAD-specific, cholesterol-independent pleiotropic effects of statins are also well known and include improvements in leg functioning, ankle-brachial index, walking performance, symptoms of claudication, and perioperative and long-term mortality.<sup>50-52</sup> Thus, statins serve as the primary foundation for effective lipid reduction in patients with PAD.

**Choice of agent and dosage.** Statins range in potency, reducing LDL between 20% and 55% (Table II).<sup>53,54</sup> The choice of which statin to initiate is determined by cost, availability within a formulary, potency, and effects on other triglyceride and HDL levels. Currently, three statins are available generically: lovastatin (Mevacor, Merck & Co Inc, Whitehouse Station, NJ), pravastatin (Pravachol, Bristol-Myers Squibb, New York, NY), and simvastatin (Zocor, Merck & Co, Inc). Atorvastatin (Lipitor, Pfizer Inc, New York, NY) retains a lead in overall United States sales and is slated to become available generically by 2011. Rosuvastatin (Crestor, AstraZeneca, London, United Kingdom) is the newest and most potent of the statins.

Considering potency, efficacy, and cost, we recommend simvastatin at 40 mg/d for the initiation of lipid-lowering therapy in PAD patients. A fasting lipid profile is obtained at baseline and 6 weeks. Although clear-cut data on routine monitoring do not exist, ATP III recommends follow-up every 6 weeks until LDL targets are achieved.<sup>4</sup> If

the desired LDL goal is not attained at 6 weeks, the dose may be increased to the maximum approved dose of 80 mg/d. It should be noted that the titration from simvastatin from 40 mg/d to 80 mg/d confers a small benefit of an additional 8% reduction in LDL and may increase risk of creatine phosphokinase level elevations. For the patient who fails to achieve LDL goals, options include switching to a more potent statin or adding ezetimibe at 10 mg/d (Zetia, Schering-Plough Corp, Kenilworth, NJ). A fasting lipid profile should be obtained 6 weeks after changes in medication or dose are made. Once at goal, fasting lipid levels should be monitored every 6 to 12 months.

**Side effects and contraindications.** Statins are well tolerated, with overall good patient adherence and compliance.<sup>55</sup> Side effects may include diarrhea, abdominal pain, myalgias, and elevations in liver enzymes. Rhabdomyolysis is rare. Patients should be instructed to notify you if muscle aches develop. If a myopathy develops, consideration of an alternative statin may be appropriate. Pravastatin and fluvastatin may have a lower risk of producing myopathy. Liver function tests should be obtained at baseline, 8 to 12 weeks after initiation or elevation in dose, and then annually.

**Recommendations.** We recommend simvastatin, 40 mg/d initially, with a fasting lipid profile at 6 weeks titrating upward to reach goal of an LDL <70 mg/dL. Check liver function tests at baseline and 12 weeks.

### Antiplatelet therapy

Platelets are pivotal in nearly all events leading to a cardiovascular death. Aspirin's irreversible inactivation of cyclooxygenase 1 (COX-1) prevents platelet conversion of prostaglandin H<sub>2</sub> to thromboxane A<sub>2</sub>, thus inhibiting platelet aggregation. The Antithrombotic Trialists' Collaboration analyzed the results of 195 randomized trials of antiplatelet agents use in >135,000 high-risk patients, concluding that antiplatelet treatment resulted in an overall 22% reduction in subsequent myocardial infarction (MI), stroke, or vascular death.<sup>56</sup>

The benefits of aspirin have been shown in prospective randomized trials with doses ranging from 75 to 1500 mg/d; however, higher aspirin doses seem to afford minimal further benefit at the expense of gastrointestinal intolerance. Furthermore, higher doses result in the potentially harmful reversible inhibition of endothelial cell synthesis of prostacyclin, a vasodilator and inhibitor of platelet aggregation. A recent systematic review concluded that aspirin dosages >75 to 81 mg/d provided no additive efficacy but increased risks of bleeding predominantly from gastrointestinal toxicity.<sup>57</sup> The formulation of aspirin, whether enteric-coated, buffered, or regular, does not affect the risk of clinically significant bleeding<sup>58</sup> or its efficacy in producing platelet inhibition.<sup>59</sup>

Clopidogrel is a thienopyridine that prevents platelet aggregation by irreversibly inactivating the adenosine diphosphate P2Y<sub>12</sub> receptor on the platelet surface. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial was a prospective, randomized multinational trial of aspirin (325 mg/d) vs clopidogrel (75

mg/d) in 19,185 patients with atherosclerotic vascular disease.<sup>3</sup> In the subgroup of 6452 patients with PAD, clopidogrel demonstrated a 23.8% relative risk reduction in risk of subsequent ischemic stroke, MI, or vascular death compared with therapy with aspirin at 2 years of follow-up. Although this benefit did reach statistical significance, the modest absolute improvement (annual event rate 3.71% vs 4.86%) must be balanced against the higher cost.

More recently, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial compared the effects of a dual antiplatelet therapy with clopidogrel plus low-dose aspirin vs aspirin alone (75 to 162 mg/d) on the incidence of cardiovascular events in 15,603 patients at high risk for atherothrombotic events followed up for a median of 28 months.<sup>60</sup> The primary efficacy end point, a composite of MI, stroke, or death from cardiovascular causes, was not significantly different between the two treatment arms. However, in a subset of 9478 patients with previous MI, ischemic stroke, or symptomatic PAD, combination therapy with clopidogrel plus aspirin showed a significant reduction in the rate of cardiovascular death, MI, or stroke (7.3% vs 8.8%), albeit with a significantly higher risk of transfusion-requiring bleeding.<sup>61</sup> In our opinion, the slight additive benefit is not justified by the increased economic cost and hemorrhagic risk.

A minority of patients is intolerant of aspirin (gastrointestinal upset, ulcer, reactive airway disease, urticaria, anaphylaxis). An alternative antiplatelet agent should be chosen for those patients, and clopidogrel is an obvious choice. It is also important to note that aspirin should be taken at least 2 hours before other nonsteroidal agents to prevent a potential deleterious interaction whereby aspirin's cardioprotective effects are reduced.

**Recommendations.** Our recommendation is aspirin, 81 mg/d.

### Hypertension

**Background.** Hypertension is the most common major risk factor for premature cardiovascular disease.<sup>17</sup> The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) defined hypertension as a systolic pressure >140 mm Hg and diastolic blood pressure >90 mm Hg based on the average of two or more reliable readings.<sup>17</sup> Meta-analyses of randomized studies demonstrate that lowering the blood pressure in patients with mild to moderate hypertension lowers the risk of stroke by 40% and of CAD by 16%.<sup>62</sup>

**Therapeutic goals.** The ACC/AHA 2005 guidelines for the management of patients with PAD suggest a target blood pressure of <140/90 mm Hg.<sup>1</sup> For those PAD patients with concomitant chronic kidney disease, congestive heart failure, or diabetes, the goal should be <130/80 mm Hg. Many patients will require more than one medication to achieve that goal. In fact, JNC 7 recommends the initiation of two medications if a patient's blood pressure is >20/10 mm Hg above goal.<sup>17</sup>



**Table III.** Suggested initial pharmacotherapy for peripheral artery disease patients

<i>Risk factor</i>	<i>Goal</i>	<i>Drug</i>	<i>Initial dose</i>	<i>Mortality reduction, %</i>	<i>Cost/mo<sup>a</sup></i>
Smoking	Cessation	Bupropion SR	150 mg/d × 3 d, then 150 mg BID	33	\$69.98
Platelet aggregation	Inhibition	Aspirin	81 mg/d	22 <sup>b</sup>	\$0.87
Hyperlipidemia	LDL <70 mg/dL	Simvastatin	40 mg/d	20-30	\$49.99
Hypertension	<130/80	Atenolol	25 mg/d	23	\$3.66
		Lisinopril	5 mg/d	22	\$10.99

*BID*, Twice daily; *LDL*, low-density lipoprotein.

<sup>a</sup>Values obtained from drugstore.com.

<sup>b</sup>Reduction in myocardial infarction, stroke, or vascular death.

**Pharmacotherapy.** Two medication classes provide the cornerstones for antihypertensive management in patients with PAD:  $\beta$ -adrenergic antagonists and angiotensin-converting enzyme (ACE) inhibitors. The  $\beta$ -blockers have antiarrhythmic, anti-ischemic, and antihypertensive properties and have been shown to reduce the risk of MI and death in large-scale prospective trials of patients with CAD.<sup>63</sup> In a meta-analysis of 26 such trials encompassing nearly 25,000 patients after MI,  $\beta$ -blockade provided a 23% reduction in mortality vs placebo.<sup>64</sup> Although a historic concern, there are few data to support concerns that  $\beta$ -blockers may worsen symptoms of claudication.<sup>65</sup> Contraindications to the use of  $\beta$ -blockers include sinus bradycardia, heart block greater than first degree, and uncompensated congestive heart failure. Selective  $\beta$ -blockers may be used with caution in patients with stable compensated congestive heart failure, mild to moderate chronic obstructive pulmonary disease or asthma, and diabetes mellitus.

Evidence for the use of ACE inhibitors in patients with PAD stems predominantly from the Heart Outcomes Prevention Evaluation (HOPE) trial in which 9297 high-risk patients without ventricular dysfunction were randomized to ramipril or placebo. In this study, ramipril reduced the risk of cardiovascular death, MI, and stroke by 22% during a 5-year period.<sup>66</sup> Subgroup analyses found 4051 of the 9297 patients had a history of PAD, claudication, or an ankle-brachial index <0.9. This cohort realized a similar benefit from ramipril compared with those patients without PAD *independent of the effect of ramipril on blood pressure*. The magnitude of this decrement in cardiovascular risk is equivalent to the benefit seen in other studies from  $\beta$ -blockers, aspirin, or lipid-lowering agents. The most common side effect of ACE inhibitors is a dry cough. If the patient is intolerant of ACE inhibition, therapy with an angiotensin II receptor blocker could be considered. The cardioprotective effects of angiotensin II receptor blockers are less well characterized.

**Recommendations.** We recommend starting with atenolol, 25 mg daily, and titrating upward to reach a heart rate of <80 beats/min and a blood pressure of <140/90 (130/80 in patients with diabetes, renal insufficiency, or heart failure). The maximum suggested dose of atenolol is 100 mg/d. Avoid  $\beta$ -blockade if the resting heart rate is <60 beats/min or if the patient has a conduction abnormality. Lisinopril should be initiated at a low dose (5 mg

and titrated upward to the preferred dose of 20 mg/d. The maximum suggested dose of lisinopril is 40 mg/d. It is recommended to check levels of serum creatinine and potassium 1 week after initiation of ACE inhibitors.

### Diabetes mellitus

Many patients with PAD have diabetes. Indeed, a 1% increase in hemoglobin A<sub>1C</sub> correlates with a 28% increase in PAD incidence and a 28% increased risk of death.<sup>67</sup> However, there are little data to support that aggressive control of blood glucose levels improves risk of MI, stroke, vascular death, or amputation. We believe the day-to-day management of diabetes is outside the scope of practice of most vascular surgeons. Nevertheless, suggestions for diabetic foot care and recommendation of a target hemoglobin A<sub>1C</sub> of <7% should be communicated to the primary care physician.

### CONCLUSION

Vascular surgeons are ideally positioned to intervene on risk factors in their patients with PAD and have long championed the medical care of their patients. A *vade mecum*—literally, “go with me” from modern Latin—is a guide at hand for insightful consultation. It is our hope that this article provides a germane review of the extant literature and offers vascular surgeons practical, evidence-based advice to initiate effective therapies that reduce overall cardiovascular risk in patients with PAD (Table III). These suggested protocols are broadly applicable to patients in a vascular practice, since abdominal aortic aneurysm and symptomatic carotid stenosis are also considered coronary equivalents.

The responsibility for initiating these risk reduction strategies in patients shared with a primary care physician and other cardiovascular specialists is frequently unclear or awkward; unfortunately, “divided responsibility often leads to no therapy at all.”<sup>68</sup> In the final analysis, we are physicians with specialized knowledge participating in the care of an underserved population. Despite the global recognition of the value of risk factor reduction, specific details for initiating therapy are not widely dispensed. We believe it is the obligation of the vascular surgeon to initiate these therapies at the first visit, reinforce compliance at each visit, and arrange for lifelong follow-up. Failure to make such

specific recommendations regarding therapy tacitly attenuates their value.

## REFERENCES

- Hirsch AT, Haskal ZJ, Hertzner NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *J Am Coll Cardiol* 2006;47:1239-12.
- Newman AB, Shemanski L, Manolio TA, Cushman M, Mittelmark M, Polak JF, et al. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. The Cardiovascular Health Study Group. *Arterioscler Thromb Vasc Biol* 1999;19:538-45.
- A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996;348:1329-39.
- Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-421.
- Grundey SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227-39.
- Smith SC Jr, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation* 2006;113:2363-72.
- Bianchi C, Montalvo V, Ou HW, Bishop V, Abou-Zamzam AM Jr. Pharmacologic risk factor treatment of peripheral arterial disease is lacking and requires vascular surgeon participation. *Ann Vasc Surg* 2007;21:163-6.
- Leon LR Jr, Labropoulos N, Lebda P, Kalman PG. The vascular surgeon's role in risk factor modification: results of a survey. *Perspect Vasc Surg Endovasc Ther* 2005;17:145-53.
- Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg* 2007;45(suppl S):S5-67.
- McDermott MM, Hahn EA, Greenland P, Cella D, Ockene JK, Brogan D, et al. Atherosclerotic risk factor reduction in peripheral arterial disease: results of a national physician survey. *J Gen Intern Med* 2002;17:895-904.
- Kalman PG, Irvine J, Ritvo P. How do vascular surgeons perceive atherosclerotic risk factor management? *Ann Vasc Surg* 2000;14:652-8.
- Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation* 2006;114:82-96.
- Purnell JQ, Kahn SE, Albers JJ, Nevin DN, Brunzell JD, Schwartz RS. Effect of weight loss with reduction of intra-abdominal fat on lipid metabolism in older men. *J Clin Endocrinol Metab* 2000;85:977-82.
- Jenkins DJ, Kendall CW, Marchie A, Faulkner DA, Wong JM, de Souza R, et al. Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein. *JAMA* 2003;290:502-10.
- Stefanick ML, Mackey S, Sheehan M, Ellsworth N, Haskell WL, Wood PD. Effects of diet and exercise in men and postmenopausal women with low levels of HDL cholesterol and high levels of LDL cholesterol. *N Engl J Med* 1998;339:12-20.
- Sacks FM, Katan M. Randomized clinical trials on the effects of dietary fat and carbohydrate on plasma lipoproteins and cardiovascular disease. *Am J Med* 2002;113(suppl 9B):13S-24S.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42:1206-52.
- Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation* 2004;110:738-43.
- Critchley J, Capewell S. Smoking cessation for the secondary prevention of coronary heart disease. *Cochrane Database* 2004;CD003041.
- Wilson K, Gibson N, Willan A, Cook D. Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies. *Arch Intern Med* 2000;160:939-44.
- Godtfredsen NS, Holst C, Prescott E, Vestbo J, Osler M. Smoking reduction, smoking cessation, and mortality: a 16-year follow-up of 19,732 men and women from The Copenhagen Centre for Prospective Population Studies. *Am J Epidemiol* 2002;156:994-1001.
- Bjartveit K, Tverdal A. Health consequences of smoking 1-4 cigarettes per day. *Tobacco Control* 2005;14:315-20.
- Anderson JE, Jorenby DE, Scott WJ, Fiore MC. Treating tobacco use and dependence: an evidence-based clinical practice guideline for tobacco cessation. *Chest* 2002;121:932-41.
- Fiore MC. US public health service clinical practice guideline: treating tobacco use and dependence. *Respir Care* 2000;45:1200-62.
- Lancaster T, Stead LF. Individual behavioural counselling for smoking cessation. *Cochrane Database Syst Rev* 2005;CD001292.
- Stead LF, Lancaster T. Group behaviour therapy programmes for smoking cessation. *Cochrane Database Syst Rev* 2005;CD001007.
- Stead LF, Perera R, Lancaster T. Telephone counselling for smoking cessation. *Cochrane Database Syst Rev* 2006;3:CD002850.
- Greenland S, Satterfield MH, Lanes SF. A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. *Drug Saf* 1998;18:297-308.
- Joseph AM, Norman SM, Ferry LH, Prochazka AV, Westman EC, Steele BG, et al. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *N Engl J Med* 1996;335:1792-8.
- Ford CL, Zlabek JA. Nicotine replacement therapy and cardiovascular disease. *Mayo Clinic Proc* 2005;80:652-6.
- Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2004;CD000146.
- Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;340:685-91.
- Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2007;CD000031.
- Simon JA, Duncan C, Carmody TP, Hudes ES. Bupropion for smoking cessation: a randomized trial. *Arch Intern Med* 2004;164:1797-803.
- Swan GE, McAfee T, Curry SJ, Jack LM, Javitz H, Dacey S, et al. Effectiveness of bupropion sustained release for smoking cessation in a health care setting: a randomized trial. *Arch Intern Med* 2003;163:2337-44.
- Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev* 2007;CD006103.
- Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 2006;296:47-55.
- Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 2006;296:56-63.
- Nides M, Oncken C, Gonzales D, Rennard S, Watsky EJ, Anziano R, et al. Smoking cessation with varenicline, a selective alpha4beta2 nico-

- tinic receptor partial agonist: results from a 7-week, randomized, placebo- and bupropion-controlled trial with 1-year follow-up. *Arch Intern Med* 2006;166:1561-8.
40. Tonstad S, Tonnesen P, Hajek P, Williams KE, Billing CB, Reeves KR. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA* 2006;296:64-71.
41. Wallis EJ, Ramsay LE, Ul-Haq I, Ghahramani P, Jackson PR, Rowland-Yeo K, et al. Coronary and cardiovascular risk estimation for primary prevention: validation of a new Sheffield table in the 1995 Scottish health survey population. *BMJ* 2000;320:671-6.
42. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.
43. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
44. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996;335:1001-9.
45. Tonkin AM, Colquhoun D, Emberson J, Hague W, Keech A, Lane G, et al. Effects of pravastatin in 3260 patients with unstable angina: results from the LIPID study. *Lancet* 2000;356:1871-5.
46. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999;282:2340-6.
47. Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD. Cholesterol reduction yields clinical benefit: impact of statin trials. *Circulation* 1998;97:946-52.
48. Liao JK. Effects of statins on 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibition beyond low-density lipoprotein cholesterol. *Am J Cardiol* 2005;96:24F-33F.
49. Feringa HH, Karagiannis SE, van Waninge VH, Boersma E, Schouten O, Bax JJ, et al. The effect of intensified lipid-lowering therapy on long-term prognosis in patients with peripheral arterial disease. *J Vasc Surg* 2007;45:936-43.
50. McDermott MM, Guralnik JM, Greenland P, Pearce WH, Criqui MH, Liu K, et al. Statin use and leg functioning in patients with and without lower-extremity peripheral arterial disease. *Circulation* 2003;107:757-61.
51. Mohler ER 3rd, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. *Circulation* 2003;108:1481-6.
52. Mondillo S, Ballo P, Barbati R, Guerrini F, Ammaturo T, Agricola E, et al. Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. *Am J Med* 2003;114:359-64.
53. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR\* Trial). *Am J Cardiol* 2003;92:152-60.
54. Bradford RH, Shear CL, Chremos AN, Dujovne CA, Franklin FA, Grillo RB, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results: two-year efficacy and safety follow-up. *Am J Cardiol* 1994;74:667-73.
55. Pedersen TR, Berg K, Cook TJ, Faergeman O, Haghfelt T, Kjekshus J, et al. Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study. *Arch Intern Med* 1996;156:2085-92.
56. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86.
57. Campbell CL, Smyth S, Montalescot G, Steinhilber SR. Aspirin dose for the prevention of cardiovascular disease: a systematic review. *JAMA* 2007;297:2018-24.
58. Kelly JP, Kaufman DW, Jurgelson JM, Sheehan J, Koff RS, Shapiro S. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. *Lancet* 1996;348:1413-6.
59. Karha J, Rajagopal V, Kottke-Marchant K, Bhatt DL. Lack of effect of enteric coating on aspirin-induced inhibition of platelet aggregation in healthy volunteers. *Am Heart J* 2006;151:976 e977-11.
60. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354:1706-17.
61. Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. *J Am Coll Cardiol* 2007;49:1982-8.
62. Hebert PR, Moser M, Mayer J, Glynn RJ, Hennekens CH. Recent evidence on drug therapy of mild to moderate hypertension and decreased risk of coronary heart disease. *Arch Intern Med* 1993;153:578-81.
63. Hennekens CH, Albert CM, Godfried SL, Gaziano JM, Buring JE. Adjunctive drug therapy of acute myocardial infarction—evidence from clinical trials. *N Engl J Med* 1996;335:1660-7.
64. Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction. An overview of results from randomized controlled trials. *JAMA* 1993;270:1589-95.
65. Radack K, Deck C. Beta-adrenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease. A meta-analysis of randomized controlled trials. *Arch Intern Med* 1991;151:1769-76.
66. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145-53.
67. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:837-53.
68. Grundy SM, Balady GJ, Criqui MH, Fletcher G, Greenland P, Hiratzka LF, et al. When to start cholesterol-lowering therapy in patients with coronary heart disease. A statement for healthcare professionals from the American Heart Association Task Force on Risk Reduction. *Circulation* 1997;95:1683-5.

Submitted Nov 28, 2007; accepted Dec 10, 2007.